Docket No.: 1422-0708PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Yutaka HANAZONO et al.

Application No.: 10/568,502 Confirmation No.: 9981

Filed: February 16, 2006 Art Unit: 1632

For: METHOD OF DIFFERENTIATION FROM EMBRYO-STEM CELL OF PRIMATE TO HEMATOGENOUS CELL Examiner: D. Crouch

DECLARATION UNDER 37 C.F.R. § 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Dr. Yutaka HANAZONO, a citizen of Japan, having an address of 2-11-12 Gion, Shimotsuke-shi, Tochigi-ken, Japan, declares and states as follows.

I am one of the co-inventors of the subject matter of the above-identified application and have complete knowledge of all aspects of the invention embodied therein.

I graduated from Faculty of Medicine, University of Tokyo (Tokyo, Japan), in March, 1986, and completed the post graduate course in March, 1992. I was awarded the degree of Doctor of Medicine from University of Tokyo in March, 1986, and the degree of Doctor of Philosophy from University of Tokyo in March, 1992.

I am a member of Japanese Society of Hematology (Councilor), Japan Society of Gene Therapy (Councilor), Japanese Society of Internal Medicine, Japanese Cancer Association, Japanese Society for Regenerative Medicine, Japanese Society of Inflammation and Regeneration, Japanese Society of Molecular Biology, American Society of Hematology, American Society of Gene Therapy, and International Society for Stem Cell Research.

I had been a physician resident (University of Tokyo Hospital from 1986 to 1987, and Mitsui Memorial Hospital from 1987 to 1988). I had been a junior scientist in the Japanese Society for the Promotion of Science from 1991 to 1993. I had been an assistant professor of medicine, Faculty of Medicine, University of Tokyo (Tokyo, Japan), from 1993 to 1995. I had been a visiting associate of Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health (Maryland, USA), from 1995 to 1998. I had been an assistant professor, Division of Genetic Therapeutics, Center for Molecular Medicine, Jichi Medical University (Tochigi, Japan), from 1998 to 2003, and an associate professor, Division of Regenerative Medicine, Jichi Medical University, from 2003 to 2007. From April, 2007, I have been a professor, Division of Regenerative Medicine, Center for Molecular Medicine, Jichi Medical University, do declare and say as follows:

2. I have read and understand the contents of the Office Action dated March 24, 2008, issued in connection with the above-identified application.

3. I have read and understand the contents of the references cited in the March 24, 2008, Office Action, including the references of Zanjani *et al.* (*International J. Hematol.*, Vol. 63, pp. 179-192 (2001)) in view of Li *et al.* (*Blood*, Vol. 98, pp. 335-342 (1996)), Sone *et al.* (*Circulation*, Vol. 107, pp. 2085-2088 (2003)) and Hamaguchi *et al.* (*Blood*, Vol. 93, pp. 1549-1556 (1999)).

4. In the March 24, 2008, Office Action, the Examiner refers to various parts of Zanjani *et al.*, Li *et al.*, Sone *et al.* and Hamaguchi *et al.*, wherein the disclosures of the references can be combined to achieve a method that is being c laimed in the present application. However, one of ordinary skill in the art would not combine such disclosures of these references, nor would one of ordinary skill in the art achieve the claimed invention.

5. In the presently claimed invention, an embry onic stem cell is transplanted to fetal sheep so as to prepare human/sheep hematopoietic chimeras. But it is known in the art that there have been many failed attempts to achieve what is being claimed. The article by M. Kyba and G.Q. Daley (*Experimental Hematology*, Vol. 31 (11), pp. 994-1006 (2003)) confirms this understanding of the state of the art. The *Experimental Hematology* (2003) article discloses the difficulty in preparing adult hematopoietic chimeras from embryonic stem cells, as even stated in the paragraph spanning the left and right columns on page 996 (see section titled "Hematopoietic from ES cells: primitive or definitive?"):

> Since the first demonstration of blood differentiation in EBs, many groups have attempted to transplant EB-derived cells into conditioned adult recipients.

> Although the failure of EB-derived cells to generate spleen colonies (CFU-S) has been documented [24], the many failed attempts to generate adult hematopoietic chimeras for the most part have not been published. In the two decades that have passed since the initial observation of blood differentiation from ES cells, there have been a few sporadic reports of success. ...

The *Experimental Hematology* (2003) article describes that many attempts to generate adult hematopoietic chimeras have failed, wherein many of the failed attempts are not published.

6. In this particular field of technology (transplanting primate stem cells into a fetus in a uterus of a pregnant sheep and obtaining hematopoietic cells from a lamb born from the fetus), it is impossible to design an experiment and predict the results. For Example, embryonic stem cells are very sensitive to culture conditions and the culture conditions under which they are prepared prior to transplantation can have a significant effect on their ability to properly propagate. Additionally, it is virtually impossible to predict the effect that administration to the born lamb of a biologically active material, such as stem cell factor, will have on the transplanted cells.

7. I hereby declare that all statements made herein of my own knowledge are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: August 5, 2008

By: Yutaka Hanazono

Yutaka HANAZONO (Dr.)
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